PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 01 September 2000 (01.09.00)	
International application No. PCT/EP98/08199	**Applicant's or agent's file reference** 1676/PCT
International filing date (day/month/year) 14 December 1998 (14.12.98)	**Priority date** (day/month/year)
Applicant TEPIC, Slobodan	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

13 June 2000 (13.06.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Zakaria EL KHODARY

Telephone No.: (41-22) 338.83.38

EP9808199

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

LUSUARDI, Werther
DR. LUSUARDI AG
Kreuzbühlstrasse 8
CH-8008 Zürich
SUISSE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	16.03.2001
Applicant's or agent's file reference: 1676/PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP98/08199	14/12/1998	14/12/1998

Applicant
AO RESEARCH INSTITUTE DAVOS et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hundt, D Tel.+49 89 2399-8042

Form PCT/IPEA/416 (July 1992)

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
1676/PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP98/08199	14/12/1998	14/12/1998
International Patent Classification (IPC) or national classification and IPC		
A61L24/06		
Applicant		
AO RESEARCH INSTITUTE DAVOS et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 9 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13/06/2000	16.03.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Bochelen, D Telephone No. +49 89 2399 8150

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP98/08199

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:

Description, pages:

1-7,9-12,14-18	as originally filed			
8,13	as received on	14/02/2001	with letter of	12/02/2001

Claims, No.:

13- 19	as originally filed			
1-12, 20-25	as received on	14/02/2001	with letter of	12/02/2001

Drawings, sheets:

1/11-11/11	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-19, 21-25
	No:	Claims	20
Inventive step (IS)	Yes:	Claims	1-19, 21-25
	No:	Claims	20
Industrial applicability (IA)	Yes:	Claims	1-25
	No:	Claims	

2. Citations and explanations
   see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: US-A-5 588 745 (TANAKA KAZUNA ET AL) 31 December 1996 (1996-12-31)
D3: WO 97 18031 A (CEMVAC SYSTEM AB) 22 May 1997 (1997-05-22)
D4: WO 88 03811 A (EXPERIMENTELLE CHIRURGIE LAB) 2 June 1988 (1988-06- 02)

1. **Novelty (Art. 33 (1) and (2) PCT)**:

Document D1 discloses an apparatus and a method for preparing bone cement wherein a liquid monomer is stored in one container and a powdered polymer is stored in an evacuated mixing chamber (D1: col7 l1, col7 l53). The subject-matter of **claims 1-19** differs in that the outlet port of the mixing chamber is connected to a vacuum source. The subject-matter of **claims 1-19** is thus considered to be new.

The subject-matter of **claims 21 and 22** differs from the apparatus disclosed in document D1 (D1: col7 l10) in that the powder container is completely filled with the polymeric powder (**claim 21**) or in that the powder has a specific fractional porosity (**claim 22**). Therefore, the subject-matter of **claims 21-25** and of the dependent **claims 23-25** appears to be new.

The prior art discloses bone cements that fall within the scope of **claim 20** (D1: abstract, col7 l53). It is stressed that a product is not rendered new over the prior art when it is obtained with an alternative process.

2. **Inventive step (Art. 33 (1) and (3) PCT)**:

Document D4, which is considered to be the closest prior art, discloses a method and an apparatus for preparing bone cement consisting in a vacuum driven flooding of poly-methylmethacrylate beads contained in an evacuated chamber

with a monomer solution stored in a connected container (D4: p4 §3). The subject-matter of **claims 1, 2, 21 and 22** differs in that flooding is performed by an external vacuum source. The problem to be solved by the present invention may therefore be regarded as to provide an improved method for the preparation of bone cement. Document D3 discloses an apparatus where flooding is performed by an external vacuum source but requires additional mixing of the cement. The solution proposed in the application ensures an homogenous flooding of the powder without need of further mixing. Therefore, it is considered that the subject-matter of **claims 1, 2, 21, and 22** involves an inventive step. **Claims 3-19 and 22-25** are dependent on **claims 1-2** and **claims 21-22**, respectively and as such also meet the requirements of the PCT with respect to inventive step.

increase in the effective cross section and less by reduction in stress concentration which is not so much influenced by the size of pores.

From WO88/03811 TEPIC a vacuum flooding system is known which is essentially free of air inclusions, but the requirement for high vacuum in that system is technically difficult to achieve.

From WO97/18031 JONSSON a bone cement mixing device is known which uses an external vacuum source for removing the harmful gaseous form of the monomeric liquid used. Since the addition of the liquid to the powder does not result in a homogeneous bone cement mixture a special mixing device in form of an agitator is used for final mixing of the liquid with the powder.

From US 5,588,745 TANAKA ET AL. a further bone cement mixing device is known which the inflow of the liquid occurs simultaneously from the inside and peripherally through a plurality of slits. This know device has also the drawback that it uses the exhaustible vacuum of the pre-evacuated powder compartment.

Following the basic principles of the method according to the present invention - vacuum-induced flooding of the powder and draining of excess liquid - are described in detail.
In contrast to other known bone cement preparation systems, the present invention aims at avoiding inclusion of air, rather than allowing for it, and then reducing it. This is accomplished by

8 (cont.)

pre-packing the powder into a syringe, and then drawing the liquid through the powder column by vacuum. As the fluid moves into the powder column residual air in front of the flooding front is pulled away by the vacuum. The end result is that the residual air between the particles of powder is replaced by the cement liquid. The process leads to full wetting contact between the beads and the liquid, rendering any mechanical mixing superfluous.

Because of high solubility of benzoyl peroxide in MMA, benzoyl peroxide should preferably not be added in powdered form. Flooding of powder would result in a gradient of catalyst and lead to uneven polymerization. However, emulsion polymerized PMMA powders can be produced with residue of benzoyl peroxide which

achieved. Experiments have shown that permeability of the powder column to air is sufficient to allow a high capacity vacuum pump to reduce the pressure of the residual air fast enough to attain excellent results even if monomer flow is not held back by means of a valve.

A preferred embodiment of the powder container is shown in detail in figure 3. Powder container consists of a syringe 13, a two part piston 14 and 15, and an ampoule adapter 16. Adapter 16 is screwed onto the syringe 13. Construction of the adapter 16 provides for a connection between the monomer suction tube 17 and the inlet port 18, which is covered by a fine stainless steel mesh 19. When fully screwed-on, adapter 16 is hermetically sealed to the syringe 13 by a seal 20. The ampoule 21 filled with monomer 22 is opened and inserted into adapter 16 so that the suction tube 17 reaches near the bottom of the ampoule. The mesh 19 is tightly woven with sub-micron openings; this prevents even the smallest of powder particles to cross it. However, resistance to monomer flow is very low. Adapter 16 is constructed from three separate plastic components: the suction tube 17, the main body 23 and the cover plate 24, which are ultrasonically welded together with the mesh 19.

The two piston components, the cap 14, and the seals section 15, are pressed together along the perimeter 25. At this aspect the piston cap 14 is provided with micro-ribs 26 about 50 micrometers deep. ~~/Detail A/~~ This results in a controlled width gap separating the components 14 and 15. This gap is the downstream,

Claims

1. Method of bone cement preparation from a polymeric powder and a liquid component, comprising a polymerisable monomer or comonomer by the action of a catalytic system, whereby the particles of said powder component are packed in a powder container (7;35) with an inlet port (8) and an outlet port (9) and the liquid component is held in a liquid container (11), **characterized in that**

A) said powder container (7;35) is completely filled with said polymeric powder;

B) the liquid container (11) is connected to said inlet port (8); and

C) a vacuum source (10) is connected to said outlet port (9); whereby

D) the void space between said particles of said powder component is flooded by said liquid component, flowing from said inlet port (8) in the direction of said outlet port (9) by the action of the vacuum source (10).

2. Method of bone cement preparation from a polymeric powder and a liquid component, comprising a polymerisable monomer or comonomer by the action of a catalytic system, whereby the particles of said powder component are packed in a powder container (7;35) with an inlet port (8) and an outlet port (9) and the liquid component is held in a liquid container (11), **characterized in that**

A) said powder in said powder container (7;35) is packed to a fractional porosity of 0,30 to 0,43;

B) the liquid container (11) is connected to said inlet port (8); and

C) a vacuum source (10) is connected to said outlet port (9); whereby

D) the void space between said particles of said powder component is flooded by said liquid component, flowing from said inlet port (8) in the direction of said outlet port (9) by the action of the vacuum source (10).

3. Method according to claim 1 or 2, characterized in that catalytic system comprises benzoyl peroxide, said benzoyl peroxide being preferably contained within said particles.

4. Method according to one of the claims 1 to 3, characterized in that said upstream inlet port (8) and said downstream outlet port (9) of said container (7) allow for the passage of air and liquid, but not of said powder.

5. Method according to one of the claims 1 to 4, characterized in that said powder container (7;35) is inflexible, preferably in the form of a syringe (13).

6. Method according to one of the claims 1 to 5, characterized in that said powder in said powder containing compartment (35) is packed to a fractional porosity of 0,34 to 0,38.

7. Method according to claim 6, characterized in that said powder in said powder containing compartment (35) is packed to a fractional porosity of 0,35 to 0,37.

8. Method according to one of the claims 1 to 7, characterized in that said powder component is flooded by said liquid component in 15 to 60 seconds.

9. Method according to claim 8, characterized in that said powder component is flooded by said liquid component in 25 to 35 seconds.

10. Method according to one of the claims 1 to 9, characterized in that the flow of said liquid component is controlled by a valve (12) interposed between said liquid container (11) and said inlet port (8).

11. Method according to one of the claims 1 to 10, characterized in that flooding of said powder component by said liquid component is followed by swelling, draining of excess liquid component and extrusion of the mixed components.

12. Method according to one of the claims 1 to 11, characterized in that said draining of excess liquid is effected by a piston (39) contained in a vacuum pump (37).

20. Bone cement mixture obtained by the method according to one of the claims 1 to 19.

21. Apparatus for performing the method according to one of the claims 1 to 19,

characterized by

A) a powder container (7) with an inlet port (8) and an outlet port (9), said powder container (7;35) being completely filled with a polymeric powder;

B) a liquid container (11), whereby said liquid container contains a liquid component comprising a polymerisable monomer or comonomer; whereby

C) said liquid container (11) is connectable to said inlet port (8);

D) said outlet port (9) is connectable to a vacuum source (10); and;

E) the void space between said particles of said powder component is floodable by said liquid component through said inlet port (8) in the direction of said outlet port (9) by the action of the vacuum source (10).

22. Apparatus for performing the method according to one of the claims 1 to 19,

characterized by

A) a powder container (7) with an inlet port (8) and an outlet port (9), said powder container (7;35) containing a polymeric powder, whereby said powder in said powder container (7;35) is packed to a fractional porosity of 0,30 to 0,43;

B) a liquid container (11), whereby said liquid container contains a liquid component comprising a polymerisable monomer or comonomer; whereby

C) said liquid container (11) is connectable to said inlet port (8);

D) said outlet port (9) is connectable to a vacuum source (10); and;

E) the void space between said particles of said powder component is floodable by said liquid component through said inlet port (8) in the direction of said outlet port (9) by the action of the vacuum source (10).

23. Apparatus according to claim 21 or 22, characterized in that it comprises a vacuum source (10).

24. Apparatus according to claim 23, characterized in that said vacuum source (10) is an evacuated can (44).

25. Apparatus according to claim 23, characterized in that said vacuum source (10) is an evacuated piston (45).

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
DR. LUSUARDI AG
Attn. Lusuardi, W.
Kreuzbühlstrasse 8
CH-8008 Zürich
SWITZERLAND

	Date of mailing *(day/month/year)* 20/08/1999
Applicant's or agent's file reference 1676/PCT	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/EP 98/ 08199	International filing date *(day/month/year)* 14/12/1998
Applicant AO RESEARCH INSTITUTE DAVOS et al.	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Jaap Hurenkamp

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

TENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
1676/PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 98/ 08199	14/12/1998	
Applicant		
AO RESEARCH INSTITUTE DAVOS et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of X sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

[ ] None of the figures.

[X] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International Application No
EP 98/08199

A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L A61B B01F A61C A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 588 745 A (TANAKA KAZUNA ET AL) 31 December 1996 (1996-12-31) column 2, line 17-24 - column 3, line 10-17,44,45 column 4, line 19-28 abstract; figure ---	1,21,22
Y	US 4 808 184 A (TEPIC SLOBODAN) 28 February 1989 (1989-02-28) abstract column 1, line 15-41 - column 2, line 28-36 column 3, line 52-59; claim 2 --- -/--	1-6,8,9, 13,17-22

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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International Application No
[redacted]/EP 98/08199

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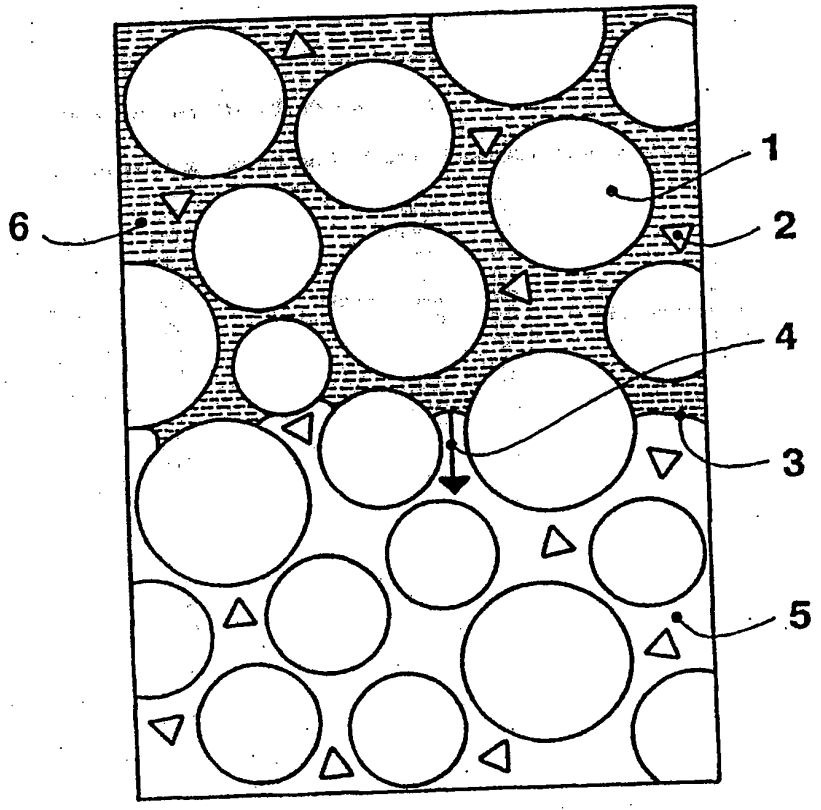
(54) Title: METHOD OF BONE CEMENT PREPARATION

(57) Abstract

The invention relates to a method of bone cement preparation from a polymeric powder and a liquid component, comprising a polymerisable monomer or comonomer by the action of a catalytic system. The particles of said powder component are packed in a powder container (7) with an inlet port (8) and an outlet port (9) and the liquid component is held in a liquid container (11). The liquid container (11) is connected to said inlet port (8) and a vacuum source (10) is connected to said outlet port (9). The void space between said particles of said powder component is flooded by said liquid component, flowing from said inlet port (8) in the direction of said outlet port (9) by the action of the vacuum source (10). The invention allows for preparation of a pore–free, mechanically superior bone cement, in a closed system that requires minimal human intervention, and delivers a consistent, operator–independent performance.



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Method of bone cement preparation

This invention relates to a method of bone cement preparation according to the preamble of claim 1. It further relates to a bone cement mixture obtained by said method according to the preamble of claim 20 and an apparatus for performing said method according to the preamble of claim 21.

The invention allows for preparation of a pore-free, mechanically superior bone cement, in a closed system that requires minimal human intervention, and delivers a consistent, operator-independent performance.

Surgical bone cement is commonly used for fixation of joint prosthesis, most frequently in total hip and total knee replacement. It is prepared by mixing a powder component, comprising emulsion polymerized polymethylmethacrylate (PMMA), with a methylmethacrylate (MMA)-based liquid. The conventional catalytic system for the room temperature curing resins is based on the chemical decomposition of benzoyl peroxide by an accelerator, N,N-dimethyl-p-toluidine. Decomposition of benzoyl peroxide releases free (phenyl) radicals and initiates polymerization of MMA. Benzoyl peroxide is either residual, i.e. left over from the

polymerization of the PMMA powder, or is added in powder form to PMMA. The accelerator is added to MMA liquid, which, at the least, also contains radical scavenger hydroquinone to prevent accidental polymerization.

In conventional bone cements, introduced to total hip replacement (THR) surgery by Dr. John Charnley in the early sixties, the powder and the liquid components are mixed together, either by a spatula in a simple bowl, or in dedicated mixing/delivery devices. Increase in the clinical use of dedicated mixing devices has been driven by mostly two factors: (i) hand mixing in open air leads to air bubble inclusions which significantly reduce the strength of bone cement; (ii) undesirable exposure of the operating room personnel to monomer vapours. Pores within the bone cement mantle, caused mostly by inclusion of air bubbles during mixing, reduce its fatigue strength, which is now generally accepted to be a major risk factor in aseptic loosening of cemented prosthetic components.

Mixing of the powder and the liquid aims at full wetting of the powder, i.e. all beads should be surrounded by the liquid. Upon decomposition of benzoyl peroxide and release of free radicals, monomer polymerizes with nucleation on the partially dissolved surface of the beads. The amount of monomer relative to powder is thus determined by predominantly physical, rather than chemical considerations. Three characteristics of polymerization effect the outcome and set the limitations on the possible improvements.

Polymerization is:

(i) exothermic:

polymerization of MMA into PMMA releases a fixed amount of heat per mole (55,6 kJ/mol). Release of polymerization heat could increase the temperature of the bone cement mixture by more than 100 deg C, but due to heat transfer into surrounding tissues and the prosthesis, temperatures at the interface to bone rarely exceed 60 deg C. The ratio of monomer to polymer is an important factor influencing final temperature increase. Less monomer to polymerize means less heat released, and the more polymer there is to warm up, the lower the temperature. Bone cement according to this invention uses about 20 % less monomer than conventional hand mixing formulations, which results in reduced peak temperatures (by about 8 degrees C).

(ii) density increasing:

density of MMA monomer is 943 kg/m^3, density of the polymer is 1180 kg/m^3, i.e. polymerization is associated with volumetric shrinkage of about 20 %. With a typical ratio of polymer to monomer of 2,1:1, this leads to an expected cured cement shrinkage of about 6,5 %. However, the ultimate, experimentally measurable, volumetric shrinkage depends on other factors, most importantly on the amount of pores within the cement. Presence of pores allows for shrinkage to be compensated from within, i.e. the pores get larger and the volume change measured from outside is less than if the cement were pore-free. In general, all methods deployed to reduce cement porosity lead to an increase in shrinkage. Reduced use of monomer in the cement of

this invention is of an advantage here as well; about 1 % less shrinkage is expected, other factors (i.e. cement and sample preparation technique) being the same.

(iii) incomplete:

polymerization process depends on formation of free radicals to initiate it, nucleation on the extant polymer surfaces and availability of monomer molecules to extend the growing chains. In all cases, a number of monomer molecules will not find their way into polymer chains and will thus remain as residual monomer within the polymerized matrix. Polymerization process will continue at a very limited rate even after most of the polymer matrix is formed due to mobility of monomer molecules through the polymerized matrix. That same mobility allows monomer to leach out of the cured cement. This is deemed undesirable in view of tissue compatibility. The range of residual monomer found in commercial cements right after preparation is about 2 to 6 % (monomer weight per total weight). In time (with quasi-equilibrium reached in 2 to 4 weeks) this is reduced to less than 0,5 % due to combined effects of continuing polymerization, migration and release of free monomer. Again, reduced use of monomer in the cement of this invention is of an advantage here as well; less monomer to start with leads to a lower residue (about 20 % compared to the best selling regular viscosity cement).

In the early eighties the shortcomings of hand mixing and delivery of bone cement became widely acknowledged. With the first long term studies of improved cementing techniques becoming

available, showing better clinical results than traditional hand mixing / hand application, the interest for, and clinical use of various systems for bone cement preparation has been steadily increasing. Disappointments with the clinical outcomes of cementless prosthesis have also contributed to re-establishment of cemented total joint replacement as a standard procedure, especially for the femoral component of the total hip replacement and for total knee prosthesis.

All known, commercially available and clinically used mixing systems are designed to remove air inclusions which are invariably introduced at the time when the liquid and powdered components are brought into contact. This task can only be partially accomplished due to mostly time limitations imposed by dissolution of PMMA in MMA and kinetics of polymerization.

Centrifuging:

Championed by Dr. William Harris, Boston, centrifuging was found to be partially effective in reducing the porosity of certain commercial brands of bone cement. While centrifuging could be used with some of the existing cements, it required cumbersome equipment, chilling of cement (to reduce viscosity and prolong setting time) and tight coordination of operating room personnel. It has found rather limited clinical acceptance in the U.S. and even less in Europe. The use of the bottom-up filling technique for the femur by means of a caulking gun, syringe and a long nozzle, as well as pre-plugging of the femoral canal to allow for cement pressurizing have also been introduced by Dr.

Harris. Currently, both, the older top-down and the bottom-up filling technique are used in Europe; in the U.S. the latter is dominant.

Partial vacuum mixing:

Developed and brought into clinical use by Dr. Lars Lidgren, Lund, this technique was adopted from the dental field where the same materials have been used for decades before introduction into orthopaedics. In molding of dentures from MMA/PMMA resins, air entrapment has also been recognized as undesirable; here less for reduction of strength than for difficulties of hygiene maintenance in dentures with pores which may be open to the surface. Mixing the cement in a bowl under partial vacuum (of some 100 mbar) reduces the porosity of the material cured at atmospheric, or elevated pressure. Partial vacuum mixing systems have found the widest clinical acceptance. Regular viscosity cements, such as Palacos R, are usually chilled (to reduce viscosity and prolong the setting time) for preparation in these systems and for extrusion through the nozzle in bottom-up delivery.

Laboratory tests show improved fatigue properties of partial vacuum mixed cements, but clinical long term studies do not support expectations. The reasons for this are obscure at the moment, but there are indications that the learning curve in the widespread use of partial vacuum mixing systems may explain this discrepancy; surgery departments that have used such systems for longer times show better outcomes than the newcomers.

Pre-pressurizing:

Developed by Dr. K. Draenert, Munich, pre-pressurizing of the bone cement aims at reducing porosity by prolonged application of pressure onto the mixed cement. While the pores are reduced during the application of pressure within the syringe, most of the effect is lost upon extrusion of the cement into the bone, where it cannot be substantially pressurized. Some benefit could be expected due to expansion of pressurized air within the pores in terms of compensating for the polymerization shrinkage, but this is very much subject to timing and viscosity of the cement. Overall, pre-pressurizing is probably the least effective measure for porosity reduction (even in laboratory tests done under optimal conditions). Dr. Draenart has subsequently expanded his original system to incorporate partial vacuum mixing, as well as pre-pressurizing.

Clinical practice, is dominated by various systems for partial vacuum mixing. The basic limitation is imposed by the level of vacuum under which mixing can be carried out. At room temperature, MMA monomer will boil at 38 mbar. Most systems are designed to operate at about 100 mbar. This leaves a significant amount of residual air entrapped in the mixed cement; once the mixture is brought back to atmospheric pressure, air inclusions shrink, say by factor 10 to 20, but pores in fact do persist -- they are only reduced in size. This improves mechanical properties, including fatigue strength, but mostly by the

increase in the effective cross section and less by reduction in stress concentration which is not so much influenced by the size of pores.

From WO88/03811 TEPIC a vacuum flooding system is known which is essentially free of air inclusions, but the requirement for high vacuum in that system is technically difficult to achieve.

Following the basic principles of the method according to the present invention - vacuum-induced flooding of the powder and draining of excess liquid - are described in detail.
In contrast to other known bone cement preparation systems, the present invention aims at avoiding inclusion of air, rather than allowing for it, and then reducing it. This is accomplished by pre-packing the powder into a syringe, and then drawing the liquid through the powder column by vacuum. As the fluid moves into the powder column residual air in front of the flooding front is pulled away by the vacuum. The end result is that the residual air between the particles of powder is replaced by the cement liquid. The process leads to full wetting contact between the beads and the liquid, rendering any mechanical mixing superfluous.

Because of high solubility of benzoyl peroxide in MMA, benzoyl peroxide should preferably not be added in powdered form. Flooding of powder would result in a gradient of catalyst and lead to uneven polymerization. However, emulsion polymerized PMMA powders can be produced with residue of benzoyl peroxide which

upon dissolution of the surface layer of the beads becomes available for the reaction with toluidine. Use of such powders with sufficient residue of benzoyl peroxide (with an average value in the range of 1,0 % to 2,5 %) allows for flooding of a packed powder column with only a slight gradient in concentrations of the catalytic system components.

Deployment of vacuum-induced, controlled flooding eliminates the need for mixing, and removes a major source of variability in cement preparation. Solubility of the PMMA powder leads to additional packing (consolidation) of the column after flooding, which creates a small excess of monomer at the inlet side of the syringe. This excess is expelled (back into the ampoule) by the action of a pneumatically driven piston before the cement syringe is removed from the vacuum pump and placed on the caulking gun for extrusion. Since the syringe ports for vacuum and liquid are provided with screens which do not allow any loss of powder, the action of the pneumatic piston leads to draining of the cement mixture (from any excess monomer). This also provides for the reduced ultimate content of monomer (by about 20%), which in other mixed cements must be present in excess in order to allow for better wetting.

Besides methylmethacrylate other suitable polymerisable monomers or comonomers may be used as e.g. ethyl-methacrylate or butyl-methacrylate or mixtures of such methacrylates.

The vacuum source should be able to generate a vacuum in the range of 10 to 200 mbar, preferably in the range of 50 to 100 mbar.

Brief description of the drawings

Fig. 1 is a schematic representation of the movement of the monomer flooding front through the powder column under influence of vacuum for the method according to the invention;

Fig. 2 is a schematic representation of the principal features of the powder container of the apparatus according to the invention;

Fig. 3 is a section through a preferred embodiment of the powder container of the apparatus according to the invention;

Fig. 4 is a schematic representation of the bone cement flooding on the vacuum pump;

Fig. 5. is a schematic representation of the swelling phase of the bone cement;

Fig. 6 is a schematic representation of the draining phase of the bone cement;

Fig. 7 is a schematic representation of showing the bone cement extrusion;

Fig. 8 is a section of the powder container with a valve of the apparatus according to the invention;

Fig. 9 is a schematic representation of an evacuated can as the source of vacuum for the method according to the invention;

Fig. 10 is a schematic representation of a pre-evacuated package with a vacuum reservoir for use with the method according to the invention; and

Fig. 11 shows a Weibull plot for the tensile strength of the bone cement obtained by the method according to invention vs. PALACOS R.

The principal process of bone cement preparation according to the present invention is orderly replacement of the residual air in the interspaces of the powder component by the liquid component. During this so-called flooding phase, Figure 1, the powder column with PMMA beads 1 and additives 2 (such as zirconium dioxide and antibiotic) is divided in two sections separated by the flooding front 3. Flooding front 3 sweeps the volume of the powder in the direction 4 driven by a pressure gradient created

by reduced pressure (vacuum) in the unflooded interspaces 5 as compared to flooded interspaces 6. Experimental work has shown that creating the flooding pressure gradient by increasing the pressure of the liquid instead of reducing the pressure of the air leads to disorderly flooding, whereby the flooding front will advance unevenly and lead to entrapment of air.

In order for the flooding front 3 to completely sweep the volume of the powder container 7, Figure 2, it is necessary to maintain evacuation of the unflooded interspaces 5 throughout the flooding phase. Hence the container 7 is provided with two ports: an inlet or upstream port 8 and an outlet or downstream port 9. Both ports must be designed so as to effectively confine the powder to the container 7 prior to and during cement preparation. Additionally, the inlet port 8 must allow for relatively easy flow of monomer, and the outlet port 9 for easy flow of air.

Flooding is effected by connecting the outlet port 9 to a vacuum source 10 and the inlet port 8 to a monomer container 11. Since no mixing is needed for a PMMA based bone cement prepared according to this invention, container 7 is preferably inflexible and completely filled with powder. Inlet port 8 may optionally be supplied by a valve 12, which is operated either manually or automatically, responding to the pressure difference between the evacuated powder container 7 (at the inlet port 8) and the monomer container 11 (which is essentially at the atmospheric pressure). The valve 12 could be used to prevent the flow of monomer before a certain level of vacuum in the powder is

achieved. Experiments have shown that permeability of the powder column to air is sufficient to allow a high capacity vacuum pump to reduce the pressure of the residual air fast enough to attain excellent results even if monomer flow is not held back by means of a valve.

A preferred embodiment of the powder container is shown in detail in figure 3. Powder container consists of a syringe 13, a two part piston 14 and 15, and an ampoule adapter 16. Adapter 16 is screwed onto the syringe 13. Construction of the adapter 16 provides for a connection between the monomer suction tube 17 and the inlet port 18, which is covered by a fine stainless steel mesh 19. When fully screwed-on, adapter 16 is hermetically sealed to the syringe 13 by a seal 20. The ampoule 21 filled with monomer 22 is opened and inserted into adapter 16 so that the suction tube 17 reaches near the bottom of the ampoule. The mesh 19 is tightly woven with sub-micron openings; this prevents even the smallest of powder particles to cross it. However, resistance to monomer flow is very low. Adapter 16 is constructed from three separate plastic components: the suction tube 17, the main body 23 and the cover plate 24, which are ultrasonically welded together with the mesh 19.

The two piston components, the cap 14, and the seals section 15, are pressed together along the perimeter 25. At this aspect the piston cap 14 is provided with micro-ribs 26 about 50 micrometers deep, Detail A. This results in a controlled width gap separating the components 14 and 15. This gap is the downstream,

or outlet port 9 from the powder compartment 7 of Figure 2. The mesh 19 corresponds to the upstream, or the inlet port 8 of figure 2.

Piston is sealed inside the syringe 13 by two lips 27 and 28. The cylindrical sections 29 and 30 of the piston cap 14, and 31 and 32 of the seals section 15, form a labyrinth which prevents easy spilling of any monomer which may enter the piston at the end of flooding phase. The bottom section 33 of the syringe 13 is sealed into the vacuum pump which evacuates the powder column in the powder compartment 35 of the syringe 13, as indicated by arrows 34. Monomer flow is indicated by arrows 36.
Powder column in the powder compartment 35 is packed to a pre-determined density. Since permeability of the column depends on the fractional porosity P and on the total surface S of the particles in a unit volume according to Kozeny's equation:

$$k = 1/5\ [P^3/(1-P)^2]/S^2$$

it is important to control the powder packing process. If the powder were loosely packed it could undergo further compaction in transport and handling which would lead to uneven flooding; too tight packing would slow down flooding. Powder bead size distribution must also be precisely controlled; very fine, dust like particles of PMMA are not permitted, less monomer viscosity would increase too quickly and prevent complete flooding.

Bone cement formulation which was selected for the procedure, contains 10 % by weight of zirconium dioxide and approximately 2,5 % of Gentamycin sulphate. Optimal packing results in a powder

column of fractional porosity P = 0,36 and leads to about 30 seconds flooding time for 63 grams of powder. Acceptable range for P is 0,34 to 0,38.

A preferred method of preparation of the bone cement comprises a four step procedure:

Step 1: Flooding

Monomer ampoule 21 is opened, placed within the adapter 16, and the whole assembly is then connected to a vacuum source, e.g. a compressed air-driven (Venturi type) vacuum pump 37, Figure 4. Vacuum pump 37 is turned on initiating flooding phase which lasts on average 30 seconds.

Step 2: Swelling

Vacuum pump is turned off once the whole powder column has been flooded. Viscosity of the monomer reaching the outlet port 25 is increased and the flow of monomer through the gap between piston components 14 and 15 is very much slowed down. Thus the timing of the vacuum switch is not critical; some monomer is allowed to enter the labyrinth of the piston. Once the flooding is complete, the syringe is left in place for a pre-determined time (of 1,5 to 3,0 minutes, depending on the room temperature) of the waiting phase. During this time PMMA swells and dissolves in MMA. This releases benzoyl peroxide and initiates polymerization. Increased viscosity of the monomer due to dissolved polymer facilitates later extrusion of the cement mass; without this, rheological properties of the cement would resemble those of a

wet sand. During swelling phase powder also settles down leaving an excess of monomer 38 at the top of the syringe as shown in figure 5.

Step 3: Draining

The excess monomer 38 collected at the top of the syringe, as well as minor air bubbles produced in the very early flooding, is returned through the mesh 19 back into the ampoule 21 by the action of a piston 39 in the pump 37, Figure 6. Since neither the mesh 19 nor the piston gaps 25 allow escape of the powder particles, only the monomer is squeezed out from the cement mass as the piston 14/15 is advanced into the syringe 13. This phase, of about 15 to 30 seconds, is defined as draining. Note the principal difference to pressurizing as proposed by Draenart; in pressurizing no fluid is allowed to leave the cement mass.

Step 4: Extrusion

Once the excess monomer has been returned to the ampoule, adapter is removed from the syringe and disposed (covering the bottom with a disposal cap 40), a nozzle 41 is placed onto syringe 13, and the cement is extruded using a caulking gun 42 as shown in figure 7.

If the flooding is allowed to start with the first drop in pressure between the inlet port and the ampoule, some air will be trapped in the initial seconds of flooding. Most of it is expelled during draining. This initial entrapment of air can be reduced by a valve 43 inserted in the path of monomer, Figure 8.

If this valve is opened with a delay of say 15 to 30 seconds after the vacuum is applied to the bottom of the syringe, monomer will start flooding of the powder column containing less residual air. A technically attractive placement of the valve is in the suction tube 17. The valve could also be made to open, mechanically or by rupture, by the pressure difference between the powder compartment and the ampoule.

An alternative to the vacuum pump is an evacuated can 44, Figure 9. Evacuated to say below 1 mbar, the volume of such a can sufficient to drive the flooding is 0,3 to 0,5 liters. Such cans could be supplied sterile for single use, eliminating the need for cleaning and sterilization of (as well as the investment into) a vacuum pump. In this case draining operation could be performed by the caulking gun prior to extrusion.

A method for preparing bone cement known from WO88/03811 TEPIC requires a high level of vacuum in the powder column in order to avoid incomplete flooding. Provision of two ports (8 and 9, Figure 2) on the powder container, as in the current invention, and change in the basic concept of filling empty space by monomer to that of replacing residual air by monomer, allows for an integral source of vacuum -- an enlarged piston 45, Figure 10. Evacuation of the system could be effected through the inlet port which should then be sealed off, e.g. by a valve 43.

Advantages of the current invention have been demonstrated by extensive testing of mechanical and chemical properties of the bone cement prepared according to the invention. For comparison, most of the commercially available brands have been tested, as well as some preparations of bone cements based on the same formulation, but prepared by conventional means (hand mixing and partial vacuum mixing).

Release of the monomer into the operating room compared with the open, spatula-and-bowl mixing procedure, followed by kneading, is 60 times lower. Compared to a conventional partial vacuum mixing system, the release is 4 times lower. As commented earlier, the peak temperature is reduced by about 8 degrees C; shrinkage by about 1 % absolute, i.e. by about 20 % relative; residual monomer by about 20 %.

Tensile strength was measured to be 65 MPa compared with 40 to 55 MPa for all commercially available bone cements, hand mixed, or partial vacuum mixed. This is 20 to 60 % higher and approaching the ultimate tensile strength of pure, block polymerized, PMMA (70 to 75 MPa). An important difference is also the greatly reduced variability as illustrated by Weibull plots of static tensile tests (bone cement according to current invention vs. PALACOS R) as shown in figure 11.

Intrinsic (without pores) fatigue strength (in bending) matches the best commercial bone cement (PALACOS R).

Claims

1. Method of bone cement preparation from a polymeric powder and a liquid component, comprising a polymerisable monomer or comonomer by the action of a catalytic system, whereby the particles of said powder component are packed in a powder container (7) with an inlet port (8) and an outlet port (9) and the liquid component is held in a liquid container (11),

characterized in that

A) the liquid container (11) is connected to said inlet port (8); and

B) a vacuum source (10) is connected to said outlet port (9), whereby

C) the void space between said particles of said powder component is flooded by said liquid component, flowing from said inlet port (8) in the direction of said outlet port (9) by the action of the vacuum source (10).

2. Method according to claim 1, characterized in that catalytic system comprises benzoyl peroxide.

3. Method according to claim 2, characterized in that said benzoyl peroxide is contained within said particles.

4. Method according to one of the claims 1 to 3, characterized in that said upstream inlet port (8) and said downstream outlet port (9) of said container (7) allow for the passage of air and liquid, but not of said powder.

5. Method according to one of the claims 1 to 4, characterized in that said container (7) is inflexible, preferably in the form of a syringe (13), with its powder containing compartment (35) completely filled with said powder.

6. Method according to one of the claims 1 to 5, characterized in that said powder in said powder containing compartment (35) is packed to a fractional porosity of 0,30 to 0,43, preferably of 0,34 to 0,38.

7. Method according to claim 6, characterized in that said powder in said powder containing compartment (35) is packed to a fractional porosity of 0,35 to 0,37.

8. Method according to one of the claims 1 to 7, characterized in that said powder component is flooded by said liquid component in 15 to 60 seconds.

9. Method according to claim 8, characterized in that said powder component is flooded by said liquid component in 25 to 35 seconds.

10. Method according to one of the claims 1 to 9, characterized in that the flow of said liquid component is controlled by a valve (12) interposed between said liquid container (11) and said inlet port (8).

11. Method according to one of the claims 1 to 10, characterized in that flooding of said powder component by said liquid component is followed by swelling, draining of excess liquid component and extrusion of the mixed components.

12. Method according to one of the claims 1 to 11, characterized in that said draining of excess liquid is affected by a piston (39) contained in a vacuum pump (37).

13. Method according to one of the claims 1 to 12, characterized in that said inlet port (8) comprises a mesh (19) which does not allow for passage of said powder particles, but does allow for passage of said liquid.

14. Method according to one of the claims 1 to 13, characterized in that outlet port (9) comprises a narrow gap (25) which substantially blocks passage of said powder particles, but allows for passage of air and said liquid.

15. Method according to claim 14, characterized in that gap (25) is smaller than 50 μ.

16. Method according to claim 14, characterized in that gap (25) is smaller than 3 times the average diameter of said particles of said powder component.

17. Method according to one of the claims 1 to 16, characterized in that said polymerisable monomer or comonomer comprises methyl-methacrylate, ethyl-methacrylate or butyl-methacrylate or mixtures thereof.

18. Method according to one of the claims 1 to 17, characterized in that vacuum source (10) generates a vacuum in the range of 10 to 200 mbar.

19. Method according to claim 18, characterized in that vacuum source (10) generates a vacuum in the range of 50 to 100 mbar.

20. Bone cement mixture obtained by the method according to one of the claims 1 to 19.

21. Apparatus for performing the method according to one of the claims 1 to 19,

characterized by

A) a powder container (7) with an inlet port (8) and an outlet port (9), said powder container (7) containing a polymeric powder;

B) a liquid container (11), whereby said liquid container contains a liquid component comprising a polymerisable monomer or comonomer; whereby

C) said liquid container (11) is connectable to said inlet port (8);

D) said outlet port (9) is connectable to a vacuum source (10); and;

E) the void space between said particles of said powder component is floodable by said liquid component through said inlet port (8) in the direction of said outlet port (9) by the action of the vacuum source (10).

22. Apparatus according to claim 21, characterized in that it comprises a vacuum source (10).

23. Apparatus according to claim 22, characterized in that said vacuum source (10) is an evacuated can (44).

24. Apparatus according to claim 22, characterized in that said vacuum source (10) is an evacuated piston (45).

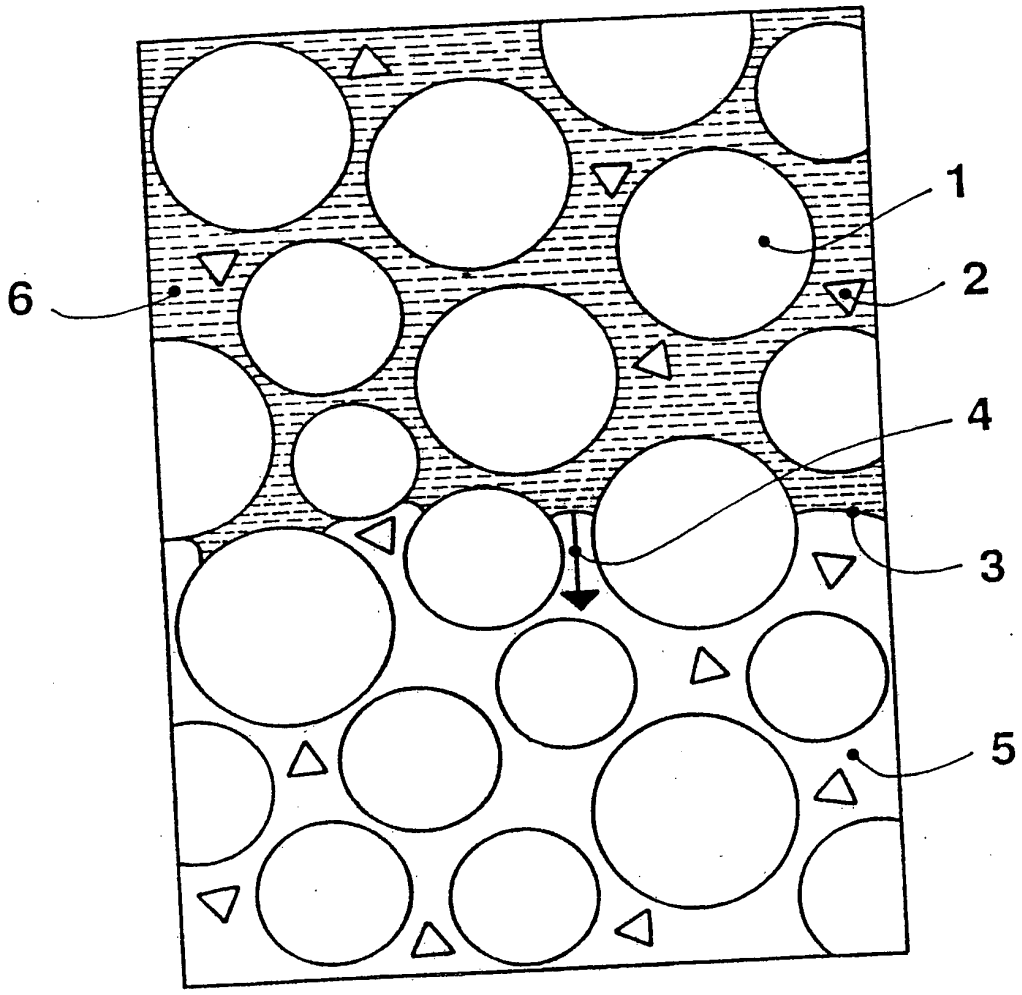

Figure 1

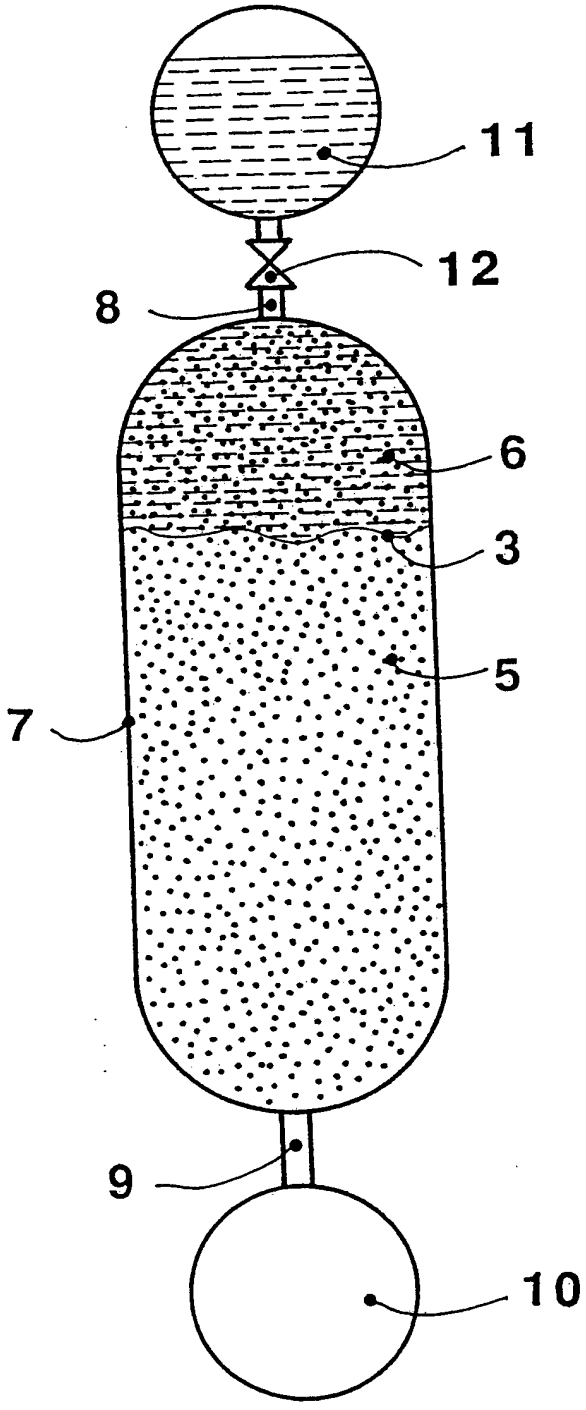

Figure 2

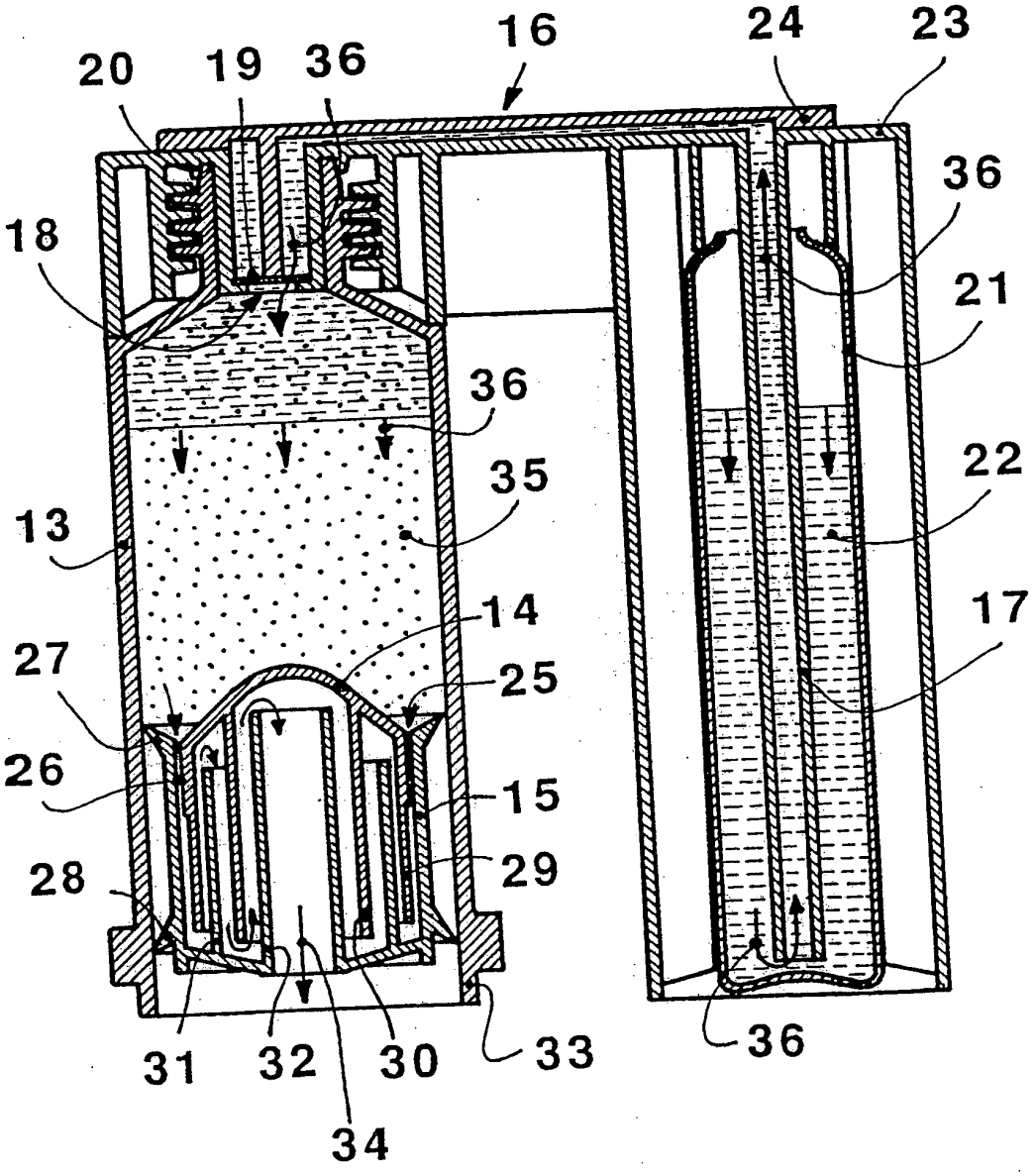
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Figure 3

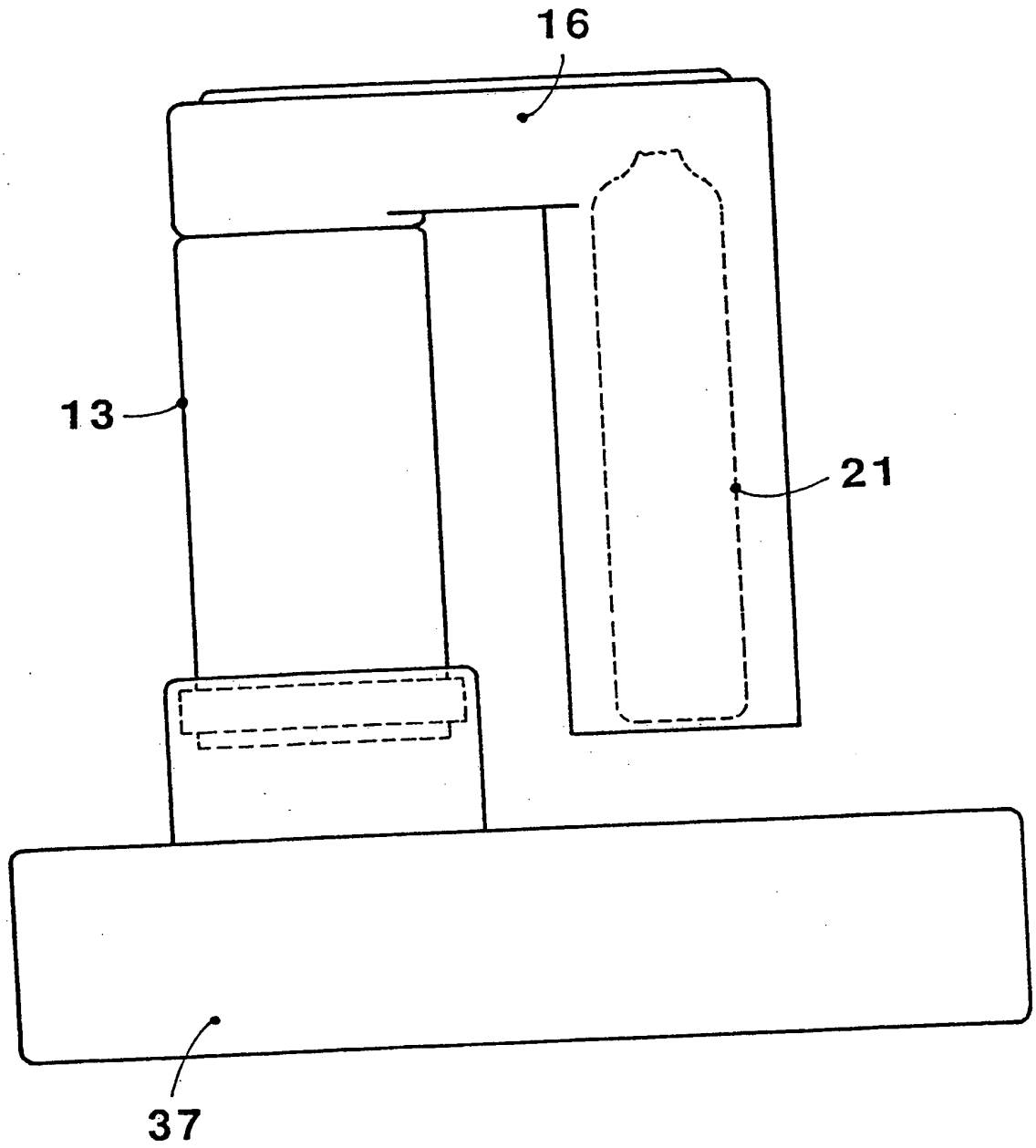


Figure 4

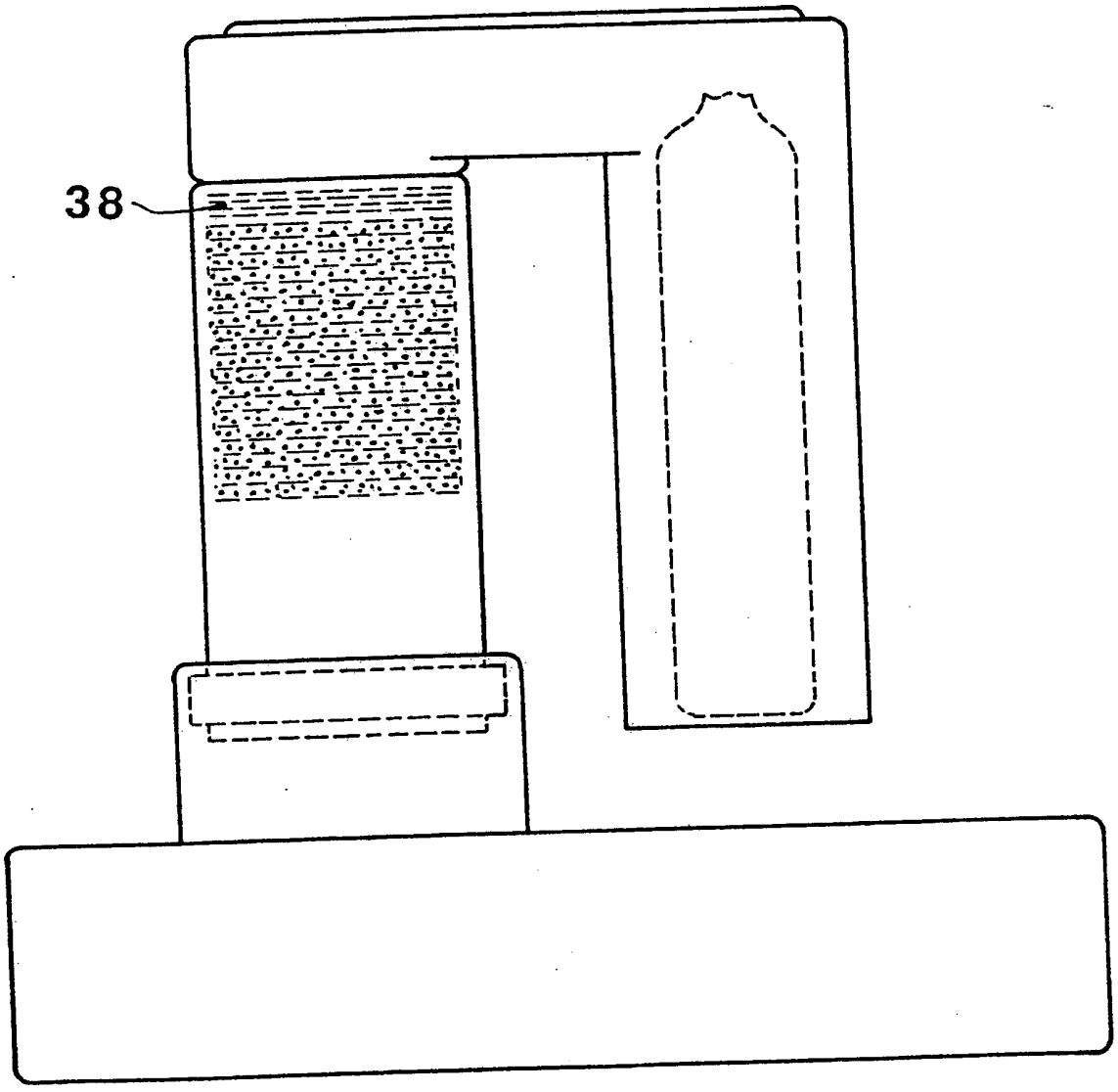


Figure 5

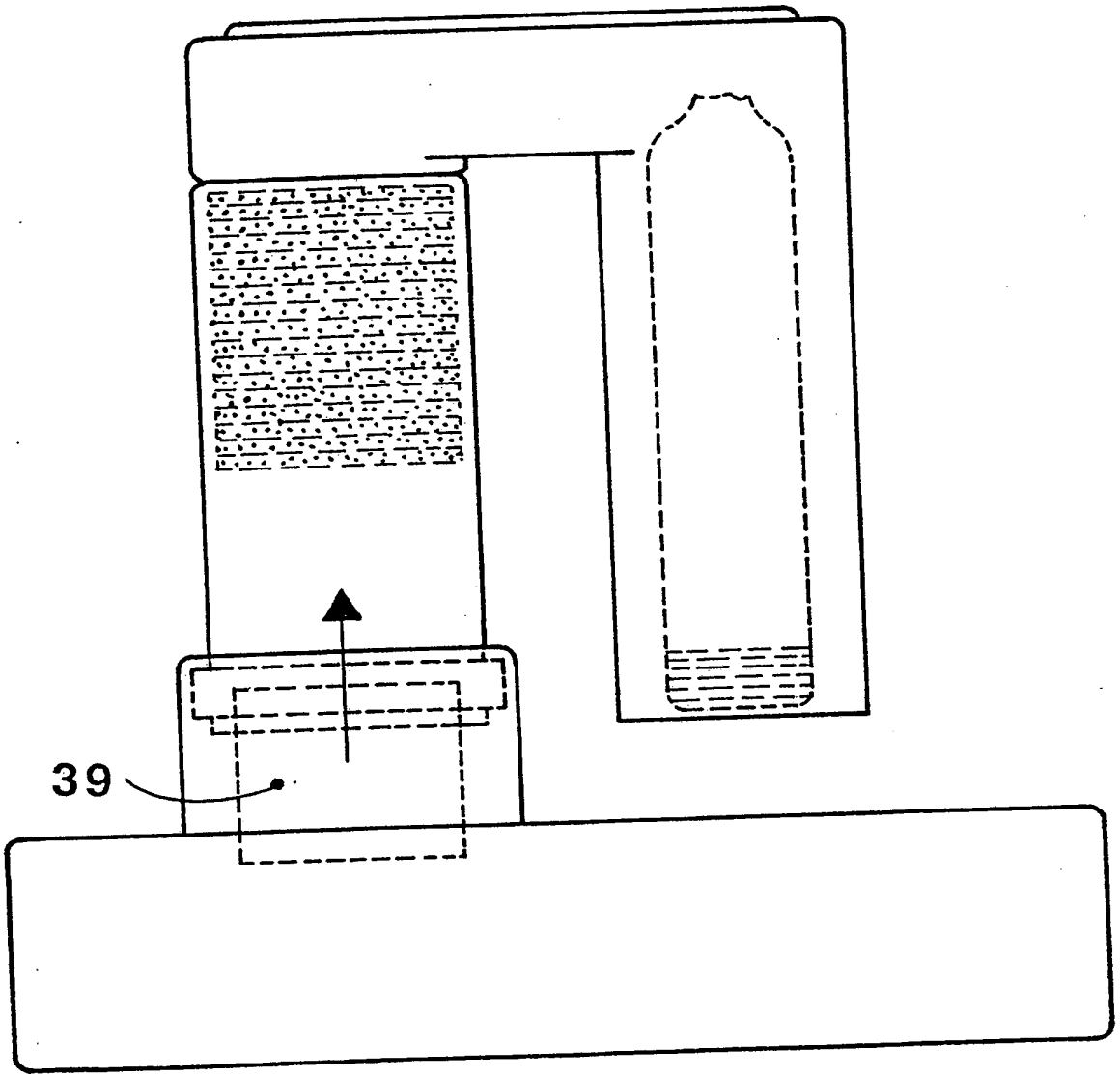
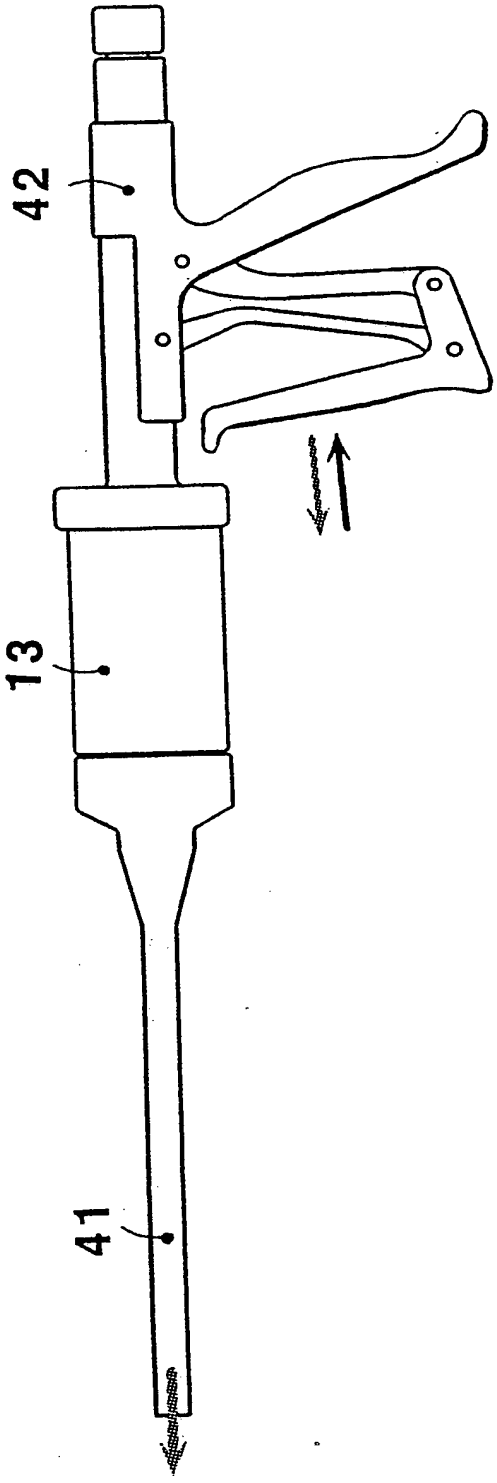


Figure 6



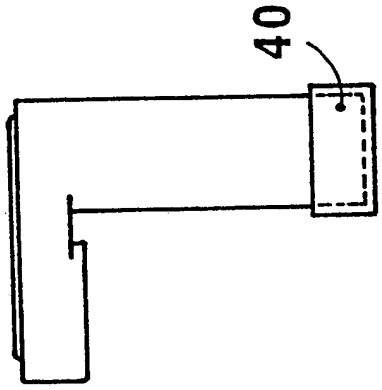


Figure 7

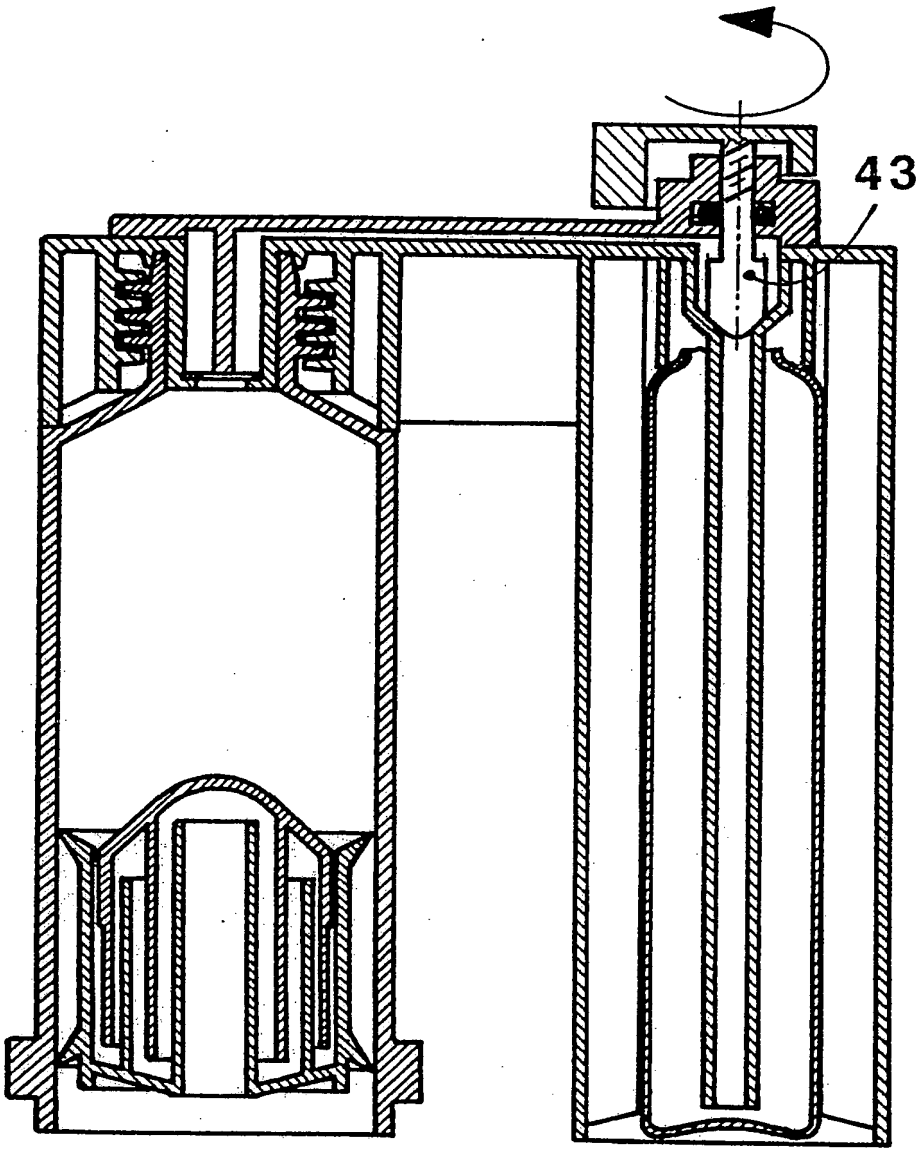


Figure 8

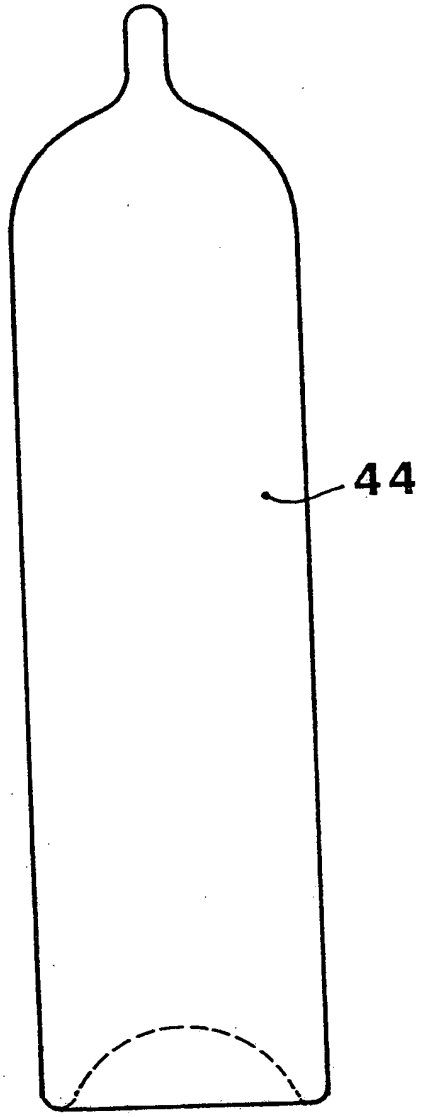


Figure 9

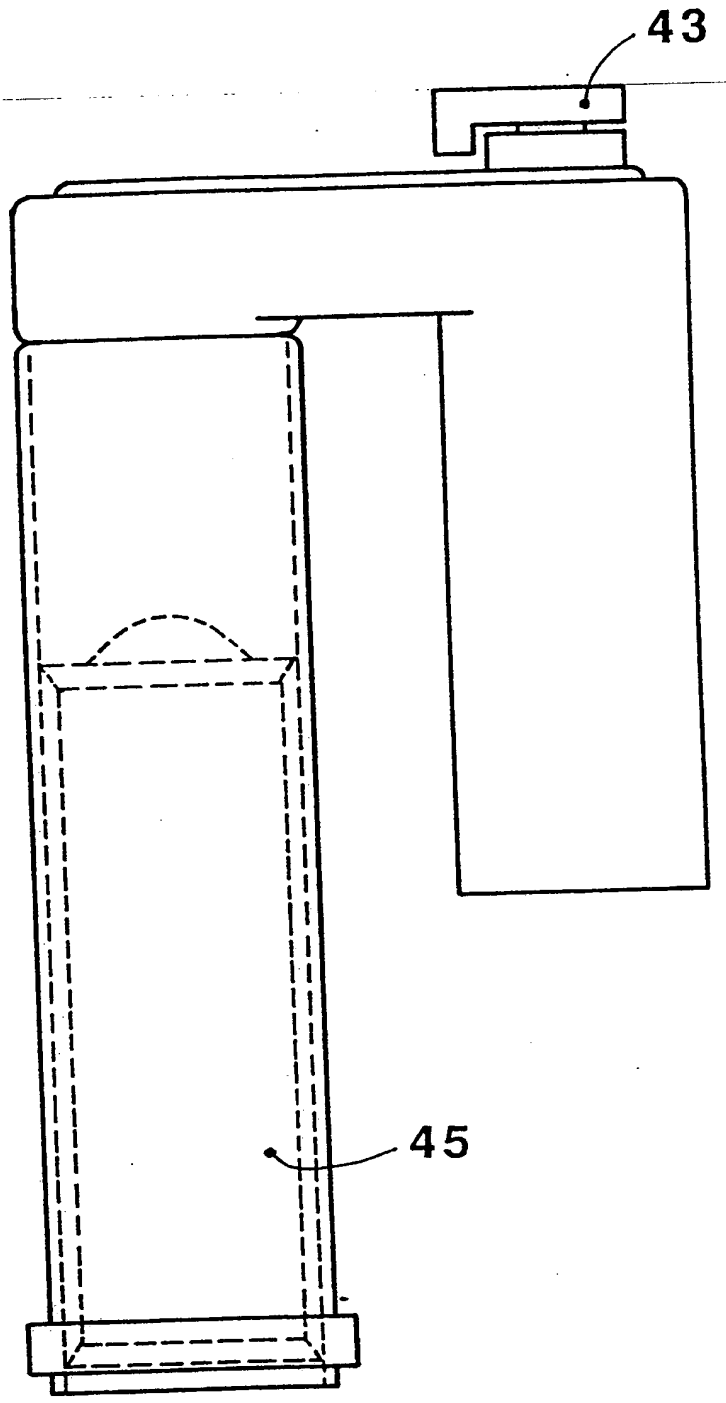


Figure 10

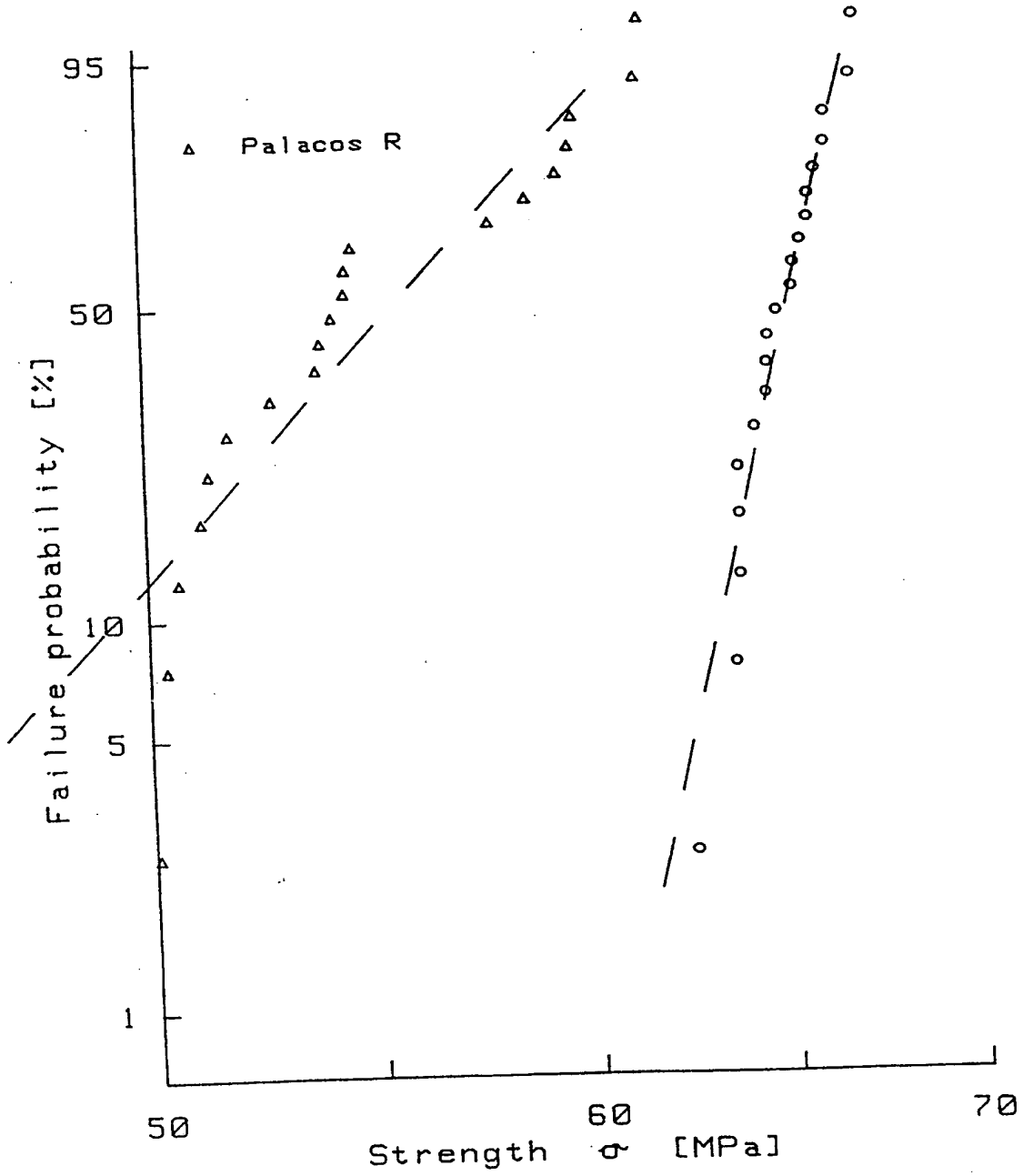

95
50
10
5
1
Failure probability [%]
Palacos R
50
60
70
Strength σ [MPa]

Figure 11

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/08199

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L24/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L A61B B01F A61C A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 588 745 A (TANAKA KAZUNA ET AL) 31 December 1996 (1996-12-31) column 2, line 17-24 - column 3, line 10-17,44,45 column 4, line 19-28 abstract; figure ---	1,21,22
Y	US 4 808 184 A (TEPIC SLOBODAN) 28 February 1989 (1989-02-28) abstract column 1, line 15-41 - column 2, line 28-36 column 3, line 52-59; claim 2 ---	1-6,8,9,13,17-22
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 August 1999	20/08/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Böhm, I

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/08199

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 18031 A (CEMVAC SYSTEM AB) 22 May 1997 (1997-05-22) abstract; figure page 1 - page 2, line 1,2,29-32 page 6, line 17-19	1,4,7, 13,17-22
Y	WO 88 03811 A (EXPERIMENTELLE CHIRURGIE LAB) 2 June 1988 (1988-06-02) abstract page 2, paragraphs 1-3; claims 3,7	1-9,13, 17,20-22
A	DE 196 41 775 A (MERCK PATENT GMBH) 26 February 1998 (1998-02-26) abstract page 2, line 1-31 - page 4, line 23-26,38	1-3,5, 17,20
A	GB 1 583 937 A (KULZER & CO GMBH) 4 February 1981 (1981-02-04) page 1, line 5-22	1-3
A	US 4 239 113 A (EGE WERNER ET AL) 16 December 1980 (1980-12-16) abstract; examples 1,6,8	1-3

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 98/08199

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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Claims

1. Method of bone cement preparation from a polymeric powder and a liquid component, comprising a polymerisable monomer or comonomer by the action of a catalytic system, whereby the particles of said powder component are packed in a powder container (7;35) with an inlet port (8) and an outlet port (9) and the liquid component is held in a liquid container (11), **characterized in that**

A) said powder container (7;35) is completely filled with said polymeric powder;

B) the liquid container (11) is connected to said inlet port (8); and

C) a vacuum source (10) is connected to said outlet port (9); whereby

D) the void space between said particles of said powder component is flooded by said liquid component, flowing from said inlet port (8) in the direction of said outlet port (9) by the action of the vacuum source (10).

2. Method of bone cement preparation from a polymeric powder and a liquid component, comprising a polymerisable monomer or comonomer by the action of a catalytic system, whereby the particles of said powder component are packed in a powder container (7;35) with an inlet port (8) and an outlet port (9) and the liquid component is held in a liquid container (11), **characterized in that**

A) said powder in said powder container (7;35) is packed to a fractional porosity of 0,30 to 0,43;

B) the liquid container (11) is connected to said inlet port (8); and

C) a vacuum source (10) is connected to said outlet port (9); whereby

D) the void space between said particles of said powder component is flooded by said liquid component, flowing from said inlet port (8) in the direction of said outlet port (9) by the action of the vacuum source (10).

3. Method according to claim 1 or 2, characterized in that catalytic system comprises benzoyl peroxide, said benzoyl peroxide being preferably contained within said particles.

4. Method according to one of the claims 1 to 3, characterized in that said upstream inlet port (8) and said downstream outlet port (9) of said container (7) allow for the passage of air and liquid, but not of said powder.

5. Method according to one of the claims 1 to 4, characterized in that said powder container (7;35) is inflexible, preferably in the form of a syringe (13).

6. Method according to one of the claims 1 to 5, characterized in that said powder in said powder containing compartment (35) is packed to a fractional porosity of 0,34 to 0,38.

7. Method according to claim 6, characterized in that said powder in said powder containing compartment (35) is packed to a fractional porosity of 0,35 to 0,37.

8. Method according to one of the claims 1 to 7, characterized in that said powder component is flooded by said liquid component in 15 to 60 seconds.

9. Method according to claim 8, characterized in that said powder component is flooded by said liquid component in 25 to 35 seconds.

10. Method according to one of the claims 1 to 9, characterized in that the flow of said liquid component is controlled by a valve (12) interposed between said liquid container (11) and said inlet port (8).

11. Method according to one of the claims 1 to 10, characterized in that flooding of said powder component by said liquid component is followed by swelling, draining of excess liquid component and extrusion of the mixed components.

12. Method according to one of the claims 1 to 11, characterized in that said draining of excess liquid is effected by a piston (39) contained in a vacuum pump (37).

20. Bone cement mixture obtained by the method according to one of the claims 1 to 19.

21. Apparatus for performing the method according to one of the claims 1 to 19,
characterized by
A) a powder container (7) with an inlet port (8) and an outlet port (9), said powder container (7;35) being completely filled with a polymeric powder;
B) a liquid container (11), whereby said liquid container contains a liquid component comprising a polymerisable monomer or comonomer; whereby
C) said liquid container (11) is connectable to said inlet port (8);
D) said outlet port (9) is connectable to a vacuum source (10); and;
E) the void space between said particles of said powder component is floodable by said liquid component through said inlet port (8), in the direction of said outlet port (9) by the action of the vacuum source (10).

22. Apparatus for performing the method according to one of the claims 1 to 19,
characterized by

A) a powder container (7) with an inlet port (8) and an outlet port (9), said powder container (7;35) containing a polymeric powder, whereby said powder in said powder container (7;35) is packed to a fractional porosity of 0,30 to 0,43;

B) a liquid container (11), whereby said liquid container contains a liquid component comprising a polymerisable monomer or comonomer; whereby

C) said liquid container (11) is connectable to said inlet port (8);

D) said outlet port (9) is connectable to a vacuum source (10); and;

E) the void space between said particles of said powder component is floodable by said liquid component through said inlet port (8) in the direction of said outlet port (9) by the action of the vacuum source (10).

23. Apparatus according to claim 21 or 22, characterized in that it comprises a vacuum source (10).

24. Apparatus according to claim 23, characterized in that said vacuum source (10) is an evacuated can (44).

25. Apparatus according to claim 23, characterized in that said vacuum source (10) is an evacuated piston (45).